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09/905,810	07/13/2001	Paul Rennert	A068 US	6397

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HADDAD, MAHER M

[REDACTED] ART UNIT [REDACTED] PAPER NUMBER

1644

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Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No.	Applicant(s)
	09/905,810	RENNERT, PAUL
	Examiner Maher M. Haddad	Art Unit 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 2/27/03.

2a) This action is FINAL.                  2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 1,4-9,12-15 and 23 is/are pending in the application.

4a) Of the above claim(s) 6-9 and 15 is/are withdrawn from consideration.

5) Claim(s) \_\_\_\_\_ is/are allowed.

6) Claim(s) 1,4-5 and 12-14 and 23 is/are rejected.

7) Claim(s) \_\_\_\_\_ is/are objected to.

8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on \_\_\_\_\_ is: a) approved b) disapproved by the Examiner.  
 If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

#### Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some \* c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

#### Attachment(s)

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____	6) <input type="checkbox"/> Other: _____

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DETAILED ACTION

1. Claims 1,4-9, 12-15 and 23 are pending.
2. Claims 6-9 and 15 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.
4. Claims 1,4-5 and 12-14 and 23 are under examination as they read on a method for blocking the development or treating or reducing the severity or effects of an immunological disorder comprising administering an antibody directed against the TWEAK ligand wherein the immunological disorder is GVHD and organ transplant failure resulting from graft rejection.
5. The priority under 35 U.S.C. § 365(b) is acknowledged and the Examiner agree with applicant's statement regarding the claimed priority under 35 U.S.C. § 365(b). No certified copy of the PCT/US00/01044 application is required, however a copy of the certified copy of the priority documents is required in this National Stage application from the international Bureau (see PCT Rule 17.2(a)).
6. The following is a quotation of the first paragraph of 35 U.S.C. 112:  
*The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*
7. Claims 1, 4-5, 12-14 and 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for blocking the development or treating or reducing the severity or effects in a subject having chronic graft-versus-host disease comprising administering anti-TWEAK ligand of SEQ ID NO: 2 monoclonal antibody, wherein said Graft-versus-Host Disease is caused by a combination of a Th1 and a Th2 cell-mediated immune response does not reasonably provide enablement for a method for blocking the development or treating or reducing the severity or effects of any GVHD in an animal comprising the step of administering any pharmaceutical composition which comprises a therapeutically effective amount of an anti-TWEAK polypeptide monoclonal antibody and a pharmaceutically acceptable carrier, wherein said Graft-versus-Host Disease is caused by a combination of a Th1 or a Th2 cell-mediated immune response alone in claims 1 and 12-13; or a method for blocking the development or treating or reducing the severity or effects of any organ transplant failure resulting from graft rejection in an animal comprising the step of administering any pharmaceutical composition which comprises a therapeutically effective amount of an anti-TWEAK polypeptide monoclonal antibody and a pharmaceutically acceptable carrier in claim 1, wherein the immune response is a Th1 cell-mediated immune response in claim 12, a Th2 cell-mediated immune response in claim 13 or both a Th1 and a Th2 cell-mediated immune response in claim 14. The specification does

not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification disclosure does not enable one skilled in the art to practice the invention as broadly claimed without any undue amount of experimentation.

The specification does not provide sufficient enablement to block/treat any GVHD caused by a Th1 cell-mediated immune response or by a Th2 cell mediated immune response alone as recited in claims 12 and 13 respectively. Dallman MJ (Current opinion in Immunology 7:632-638, 1995) teaches that Both Th1 and Th2 cells are involve in graft rejection response. Dallman concluded that it is difficult to make a case that graft rejection is caused by an immune response driven by either Th1 or Th2 cells alone (see page 632 under Does the Immune response leading to graft rejection involve both Th1 and Th2 cells? in particular). Further, as applicant indicated in the amendment filed on 2/27/03, Krenger and Ferrara (immunol. Res. 15:50-73, 1996) teach that two distinct murine models immunological patterns were observed of a acute and chronic graft-versus-host disease are associated with differential activation of Type I and type 2 T cell subsets after allogeneic BMT (see page 61, 2<sup>nd</sup> col., lines 29-33). Further, Krenger and Ferrara et al teach that a classical lethal acute GVHD is linked to the preferential activation of donor T cells secreting IL-2 and IFN-g which the less severe chronic form of GVHD is characterized a type 2 cytokine response where IL-4 and IL-10 are preferentially produced after BMT (see page 61, 2<sup>nd</sup> col., lines 38-43 and page 62, lines 1-10). Thus, the specification does not provide sufficient enablement for the treat the more severe lethal acute GVHD syndrome.

Further, at issue is whether or not the claimed method would function in “blocking the development or treating or reducing the severity or effects of an organ transplant failure resulting from graft rejection”. The difference between GVHD and organ transplant is that the rejection in GVHD is caused by the donated immune cells (the graft) that starts attacking the recipient's body (the host). While, in HVGD, the opposite occurs that is the host lymphocytes attack the graft. The nature of the invention is such that it would require the administration of anti-TWEAK antibodies to block the development of splenomegaly, activated B cells, in a murine model of chronic GVHD. The specification discloses inducing chronic GVHD in 6-8 weeks old B6D2F1 female mice then inject the mice with  $1 \times 10^8$  cells in the tail vein, wherein the mice received anti TWEAK mAb prior to graft injection to act as prophylaxis against GVHD. The exemplification is drawn to decrease in the spleen index in mice model system, as indicated by the reduced splenomegaly by 35% (1.7 compared with control 1.0) to demonstrate the ability of the anti-TWEAK to block the development of GVHD (see page 19 under example 2).

*In re Fisher*, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Since the method of prophylaxis indices of administering to the animal anti-TWEAK mAb can be species- and model-dependent, it is not clear that reliance on the mice studies of GVHD using cells accurately reflects the relative human efficacy of the claimed therapeutic strategy in organ transplants. The specification does not adequately teach how to effectively prophylaxis of HVG (organ rejection) or reach any

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therapeutic endpoint in humans by administering anti-TWEAK mAb. The specification does not teach how to extrapolate data obtained from mice studies to the development of effective in vivo mammalian including human therapeutic prevention and treatment, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of the anti-TWEAK mAb exemplified in the specification.

For example, Toogood et al (Transplantation 62:851-855, 1996) teaches that the mechanisms of rejection in small bowel and other solid organ grafts are likely to be different (see abstract in particular). Toogood et al concluded that there are significant immunological differences between the gut wall compartment of a small bowel transplant and other vascularized allografts (sse page 855, 1<sup>st</sup> col., lines 13-16 in particular). Further, in the GVHD model, donors are pretreated with the monoclonal antibodies, while in the HVGR model, recipients are treated with mAb to induce transplantation tolerance toward grafts. However, an effective preventive/treatment protocol for the prevention/treatment of organ transplant failure resulting from graft rejection is subject to a number of factors beyond simply the administration of TWEAK mAb to the donors (GVHD). The ability of a host to suppress and thereby prevent/treat organ transplant failure resulting from establishing tolerance toward grafts will vary depending upon factors such as the condition of the host and the type of grafts. Further, the specification is not enabled for organ related (allografts) or organ unrelated (xenografts), which is expected to lead to more damage or/and destruction of the grafted organs, wherein the level of immune suppression and/or rejection is expected to be greater in xenograft recipients.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Applicant's arguments, filed 2/27/03 (Paper No. 8), have been fully considered, but have not been found convincing.

Applicant argues that based on the teachings of the instant application, a person of skill in the art at the time of filling, having in hand the anti-TWEAK polypeptide mAb would immediately recognize that the mAb could be used to treat GVSD caused by a Th1 or Th2 cell-mediated immune response.

However, as applicant indicated in the amendment filed 2/27/03, Chronic and acute GVHD are considered two distinct diseases (as is evidenced Krenger and Ferrara above) and the chronic GVHD require the involvement of both Th1 and Th2 cells in graft rejection response (as is evidenced by Dallman)..

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8. Claims 1, 4-5, 12-14 and 23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a method for blocking the development or treating or reducing the severity or effects in a subject having chronic graft-versus-host disease comprising administering anti-TWEAK ligand of SEQ ID NO: 2 monoclonal antibody, wherein said Graft –Versus-Host Disease is caused by a combination of Th1 and a Th2 cell-mediated immune response.

Applicant is not in possession of a method for blocking the development or treating or reducing the severity or effects of any GVHD in an animal comprising the step of administering any pharmaceutical composition which comprises a therapeutically effective amount of an anti-TWEAK polypeptide monoclonal antibody and a pharmaceutically acceptable carrier, wherein said Graft-versus-Host Disease is caused by a combination of a Th1 or a Th2 cell-mediated immune response alone in claims 1 and 12-13; or a method for blocking the development or treating or reducing the severity or effects of any organ transplant failure resulting from graft rejection in an animal comprising the step of administering any pharmaceutical composition which comprises a therapeutically effective amount of an anti-TWEAK polypeptide monoclonal antibody and a pharmaceutically acceptable carrier in claim 1, wherein the immune response is a Th1 cell-mediated immune response in claim 12, a Th2 cell-mediated immune response in claim 13 or both a Th1 and a Th2 cell-mediated immune response in claim 14.

Applicant has disclosed only amino acid of SEQ ID NO: 2; therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. Further, Applicant has disclosed a method of treating/blocking the development of cGVHD caused by a Th1 and Th2 cell-mediated immune response; therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims and the method of treating/blocking the development of cGVHD caused by a Th1 or Th2 cell-mediated immune response alone. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics,

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sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3<sup>rd</sup> column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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May 19, 2003

  
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